REMARKS

I. Status of Claims

Claims 140-154 are currently pending. No claims have been amended herein. The pending claims are fully set forth in the Amendment filed March 24, 2004.

II. There is No Obviousness-Type Double Patenting with Respect to the Pending Claims

The Examiner has rejected claims 140-154 for obviousness-type double patenting over claims 1-19 of U.S. Patent No. 6,441,026 to Bissery ("the '026 patent"). According to the Examiner, "the currently claimed cyclopropyl taxotere has been disclosed in [the] Bissery patent which is useful to treat a variety of cancer diseases . . . ." Office Action at 2. The Examiner then concludes that "[t]here is not patentable distinctness between the current compound and the composition of Bissery since the composition is in use for medical practice and it comprises the compound (the major ingredient) and a pharmaceutical carrier(s)." *Id.* Applicants respectfully traverse and discuss herein why there is no obviousness-type double patenting with respect to the '026 patent.

In the response dated March 24, 2004, Applicants argued that the Office must provide a well reasoned basis, including application of either the one-way test or two-way test as set forth by the Federal Circuit, in for example, *In re Braat*, 937 F.2d 589, 19

U.S.P.Q.2d 1289 (Fed. Cir. 1991). The Examiner has chosen not to apply either test and has instead based his position on public policy reasons. [1]

Applicants, therefore, have sought to understand the basis of the Examiner's double patenting rejection. Upon further consideration of the law of obviousness-type double patenting, it is believed that the Office relies upon M.P.E.P. § 804 which articulates an independent public policy basis for finding obviousness-type double patenting even though a conclusion of obviousness is not compelled by the one-way or the two-way test. M.P.E.P. § 804 states

> [i]f either analysis does not compel a conclusion of obviousness, . . . this does not necessarily preclude a nonstatutory double patenting rejection based on the fundamental reason to prevent unjustified timewise extension of the right to exclude granted by a patent.

M.P.E.P. § 804 (citing *In re Schneller*, 397 F.2d 350 (C.C.P.A. 1968).

In rendering a determination of obviousness-type double patenting upon this basis, the Office, however, must necessarily evaluate whether there is justification for the extension in view of the express mandate of M.P.E.P. § 804:

> If the patent is the later filed application, the question of whether the timewise extension of the right to exclude granted by a patent is justified or unjustified **must be addressed**.

M.P.E.P. § 804 II. B(1)(b).

The Office has provided no reasoned analysis why the extension in the instant application would be unjustified beyond the conclusion, referenced above, that "[t]here is not patentable distinctness between the current compound and the composition of

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[1] A telephone conversation between Applicants' representative and the Examiner confirmed that the Office was applying neither a one-way test nor a two-way test in reaching its conclusion of obviousness-type double patenting.

Bissery since the composition is in use for medical practice and it comprises the compound (the major ingredient) and a pharmaceutical carrier(s).".[2]

Applicants have analyzed the Office's conclusion in view of M.P.E.P. § 804 II. B(1)(b) and the case law relied upon therein. Applicants, after having reviewed the legal precedent cited in that section of the M.P.E.P., conclude that no proper grounds for obviousness-type double patenting exist under that section.

In particular, *In re Schneller* is the only legal authority relied upon by the PTO in M.P.E.P. § 804 II. B(1)(b). *In re Schneller* dealt with a situation wherein in schematic terms, the Court held that a patent claim of an inventor to ABCX, containing comprising language, dominated an application claim of the same inventor to ABCY. The *Schneller* court held that the ABCX claim read on ABCXY and dominated ABCY because ABCXY was the preferred and only form disclosed by the same inventor in the patent. 397 F.2d at 355-56.

In reaching its conclusion, the *Schneller* court distinguished *In re Heinle*, 341 F.2d 1001, wherein the court held that a patent claiming a mechanical combination for holding a toilet paper roll did not create an unjustified term extension for an application claiming a single element within those recited in the patent claim. The *Heinle* court

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[2] M.P.E.P. § 804 II. (B)2 clearly states that if the Office wishes to make or maintain a rejection upon this basis, approval of the Technology Center director is required. Specifically, "[n]on-statutory double patenting rejections based upon *Schneller* **will be rare.** The Technology Center (TC) Director must approve any nonstatutory double patenting rejection based on *Schneller.* If an examiner determines that a double patenting rejection based on *Schneller* is appropriate in his or her application, the examiner should first consult with his or her supervisory patent examiner (SPE). If the SPE agrees with the examiner then approval of the TC Director must be obtained before such a nonstatutory double patenting rejection can be made." (Emphasis in the original).

reasoned that the protection of the combination afforded by the patent claim would not be extended by an application claim directed to the element. 397 F.2d at 355.

The present situation is like *Heinle*, not *Schneller*, since the patent claims the combination, and the application claims, although reciting cyclopropyl taxanes, do not recite an additional drug to be used in combination therewith. Hence, under the very case, *Schneller*, relied on by the Office in M.P.E.P. § 804 II.(B)2, the conclusion should be that there is no unjustified timewise extension and hence no obviousness double patenting rejection. For that reason alone, the rejection should be withdrawn.

Further, Applicant has considered the Office's argument that the claims of the '026 patent are not patentably distinct from those of Applicant. To be sure, there was a restriction requirement before the interference involving the present application was declared. In that restriction requirement, original claims 39-42 and 87-90, drawn to combination therapy, were grouped together with compound claims such as claims 1-4. All of the combination claims, however, were canceled without prejudice in the Request for Interference filed in April 1995.

Moreover, in fact, the claims of the '026 patent are, contrary to the Office's argument, patentably distinct from those of Applicant. That is true because in view of the instant claims, as well any relevant prior art, the claims of the '026 patent would at most have been obvious to try. Obvious to try, of course, is not a legitimate standard for assessing compliance with §103.

For example, in *In re Tomlinson*, 363 F.2d 928, 150 U.S.P.Q. 623 (C.C.P.A. 1966), the CCPA considered the patentability of an invention directed to polypropylene stabilized with a particular class of dithiocarbamates. The prior art disclosed

polyethylene stabilized with those dithiocarbamate compounds. Because of the close structural similarity between polypropylene and polyethylene, the PTO concluded that a skilled chemist would have found it obvious to try to stabilize polypropylene with a known stabilizer for polyethylene. The court responded to the PTO's position on this matter by noting that "there is usually an element of 'obviousness to try' in any research endeavor, that it is not undertaken with complete blindness but rather with some semblance of a chance of success." *Id.* at 931, 150 U.S.P.Q. at 626. Permitting patentability determinations based on an "obvious to try" test "would not only be contrary to statute but result in a marked deterioration of the entire patent system as an incentive to invest in those efforts and attempts which go by the name of 'research.'" *Id.*

Here too, the combinations recited in the claims of the '026 patent would, at most, have been obvious to try. Moreover, with respect to those combinations, the prior art, taken together with the instant claims, failed to provide a reasonable expectation of success. That reasonable expectation is one of the requirements of a *prima facie* case of obviousness, as made clear in *In re Dow Chemical Co.*, 837 F. 2d 469 (Fed. Cir. 1988).

In *Dow*, the Board held that one skilled in the art *might* have obtained the claimed polymer by applying the technique of the second reference to a styrene-maleic anhydride polymer system that included some synthetic diene rubber. In fact, the Board admitted that "[i]t is not apparent from the evidence whether rubber and maleic anhydride would have been expected to react *in the process suggested by the combined disclosure of [the cited references].*" *Id.* at 471 (emphasis in original).

In evaluating obviousness and reversing the Board, the Federal Circuit in *Dow* made it very clear that one must look to see if "the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *Id.* at 473. "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *Id.*

In the present case, one skilled in the art would have had no reasonable expectation that the cyclopropyl taxanes of claim 1 of the '026 patent could be successfully combined to exhibit efficacy with at least one of the agents named in claim 1, i.e., an alkylating agent, an antimetabolite, a spindle poison, an epidophyllotoxin, an antibiotic, an enzyme, a topoisomerase inhibitor, a platinum coordination complex, a biological response modifier and a growth factor inhibitor. The bases and reasons for that conclusion follow.

In any combination of drugs, one must first consider the effect of the combination on the efficacy of the drugs. Efficacy can be explained as follows. To demonstrate the efficacy of a combination of drugs, it may be necessary to compare the efficacy of the maximum tolerated dose of the combination with the efficacy of the maximum tolerated dose of each of the separate constituents in the study in question evaluated in the same experiment, *i.e.*, one cannot make historical comparisons. That efficacy may be quantified, for example, by the $\log_{10}$ cell kill which is determined according to the following formula:

$$\text{Log}_{10} \text{ cell kill} = T\text{-}C(\text{days})/3.32 \times T_d$$

in which T-C represents the time taken for the cells to grow, which is the mean time in days for the tumors of the treated group (T) and the tumors of the control group (C) to have reached a predetermined value (1 g for example), and T_d represents the time in days needed for the volume of the tumor to double in the control animals. See T.H. Corbett et al., *Cancer*, 40, 2660-2680 (1977) and the '026 patent at column 2, lines 12-29.

There are three possible results with respect to efficacy in combination therapy:

1) activity and synergism;

2) activity and no synergism; and

3) antagonism.

Results 1 and 2 are desirable. Result 3 is not.

Specifically, synergism is defined in the '026 patent at col. 2, lines 34 to 39 as "[T]he combination, used at its own maximum tolerated does, in which each of the constituents will be present at a dose generally not exceeding its maximum tolerated dose, will manifest therapeutic synergy when the $\log_{10}$ cell kill is greater than the value of the $\log_{10}$ cell kill of the best constituent when it is administered alone."

Activity, for a drug alone or for a combination of drugs, is also defined in the '026 patent. At col. 2, lines 29 to 31, it is stated: "[T]he product is considered to be active if $\log_{10}$ cell kill is greater than or equal to 0.7"

Antagonism means that the $\log_{10}$ cell killed for the combination is less than 0.7 or less than the log cell kill of the best single agent.

The filing date of the '026 patent was March 21, 2001. WO 94/13654, the international counterpart of the instant application, was published on June 23, 1994.

That WO document, like the instant application, discloses 4α-10β-diacetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,8β-methylene-9-oxo-19-nor-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate and suggests that it could be used in combination therapy with most of the additional pharmaceutical agents recited in claim 1 of the '026 patent. However, as explained above, no experimental results were presented in the WO document because the associated inventors had performed no such experiments.

Further, WO 94/10995, published on May 26, 1994, discloses work with Taxotere® in combination therapy.

Finally, Taxol® was administered with cisplatin, as reported in the Journal of Clinical Oncology, 99, Pp. 1692-1703, 1991,

Prior to the time the invention disclosed and claimed in the '026 patent was made, one skilled in the art would have been unable to know if the combinations disclosed and claimed would be active and synergistic, active and not synergistic, or antagonistic, without actually performing animal experiments. Hence, one skilled in the art, even having application claims and the prior art noted above in front of her and even knowing of other taxanes useful in combination therapy, would have had no reasonable expectation which of the three possible results would be obtained for the taxane combinations disclosed and claimed in the '026 patent.

Consequently, one skilled in the art would not have had a reasonable expectation of success, *i.e.,* could not have reasonably expected the desirable results of active and synergistic or active and not synergistic. At most, therefore, the combination claimed in

the '026 patent would have been obvious to try and was accordingly non-obvious over the present claims, even taken in view of the prior art cited above.

There is, therefore, no issue of obviousness-type double patenting. Thus, Applicants respectfully request withdrawal of this ground for rejection.

III. Conclusion

As the Office has already determined the subject matter of claims 140-142 to be allowable and awarded priority to Applicants over the competing claims of both Chen and Hester, and as the Office has not established that obviousness-type double patenting exists, Applicants respectfully request the prompt allowance of all of claims 140-154, including the method of use claims 143-154, which utilize the compounds of allowed claims 140 and 142.

Please grant any extensions of time required to enter this paper and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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